AF

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/717,109 | 11/19/2003 | Ram I. Mahato | T8948.CIP.2 | 7310 |

20551 7590 03/07/2006

THORPE NORTH & WESTERN, LLP.
8180 SOUTH 700 EAST, SUITE 200
SANDY, UT 84070

| EXAMINER | |
|---|---|
| SCHNIZER, RICHARD A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 03/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/717,109 | MAHATO ET AL. | |
| | Examiner | Art Unit | |
| | Richard Schnizer, Ph. D | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 11/14/03 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/20/04;2/22/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This application is a continuation in part of 10/083,861 which is a continuation in part of 09/662,511, now US 6,696,038.

Claims 1-27 are pending and under consideration in this Office Action.

### *Claim Objections*

Claims 1 and 8 are objected to because "back bone" should be a single word.

Claims 4 and 15 are objected to because "cholesterol derivatives", "$C_{12}$ to $C_{18}$ fatty acids", and "fatty acid derivatives", should each be singular, not plural.

Claim 6 is objected to because it lacks an article prior to "molar ratio".

Claim 18 is objected to. The word "comprising" should be substituted for "comprises:, and substitution of "is" for "s" immediately after "which", is suggested.

Claim 27 is objected to because oleoylpalmitoylphosphatidylaethanolamin" and "diphytanylphosphatidylaethanolamin" lack a final 'e', and because "disteroyl" is also misspelled.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 9, 10, 15, 16, 19, 20 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 15 are indefinite because the metes and bounds of "cholesterol derivatives" and "fatty acid derivatives" are unclear.

Claims 9 and 19 are indefinite because the inclusion of the word "and" immediately before "thrombomodulin" makes the nature of the Markush group unclear. Deletion of this instance of "and" is suggested.

Claims 10 and 20 are indefinite because they recite "the covalent bond" without proper antecedent basis. For claim 10, there are distinct antecedents for "covalent" in claims 1 and 8. For claim 20 there are distinct antecedents for "covalent" in claims 12 and 18.

Claim 16 is indefinite because it recites "the biocompatible hydrophilic polymer spacer" without antecedent basis.

Claim 27 is indefinite because it is unclear what is intended by "disteroyl-, palmitoyl-, myristoylphosphatidylethanolamine." If this is supposed to reflect a diacylgylcerol phospholipid, then Applicant is reminded that such compounds may have only two acyl groups.

## *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-21, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Epand et al (US Patent 5,283,185, issued 2/1/94) in view of Ogris et al (Gene therapy (1999) 6: 595-605).

Epand taught methods and lipopolymeric compositions for transferring nucleic acids into cells. See abstract, claims 1 and 10, and compound XV, described at column 9, lines 45-58. Lipopolymeric compound XV is formed by mixing cholesteryl chloroformate with PEI 600. The resulting reaction chemistry is identical to that taught in the instant application, and results in the formation of a lipopolymer with cholesterol covalently bound to PEI via an ester linkage. Compare Fig. 1 of the instant application with Fig. 3 of Epand. The composition may comprise a DOPE helper lipid in a 1:1 ratio with the cationic lipopolymer. See Table I at column 12, and column 12, lines 58-61. Epand teaches that the charge ratio of lipopolymer to nucleic acid is a result effective variable. See column 13, lines 6-11, and Fig. 5.

Epand did not teach PEI covalently modified with a biocompatible hydrophilic polymer or a targeting ligand.

Ogris taught DNA/transferrin/PEI/PEG complexes in which PEG and transferrin were independently covalently attached to primary amines of PEI. The PEG has a molecular weight of 5000 D. Approximately two thirds of the primary amino groups of PEI remained unmodified. See abstract; and paragraph bridging pages 595 and 596. Ogris taught successful delivery to tumor cells in mice by systemic administration of the complexes.

It would have been obvious to one of ordinary skill in the art the time of the invention to graft PEG to the branched lipopolymer of Epand et al, as well as to attach a targeting ligand such as transferrin. One would have been motivated to do so because Ogris teaches that covalent attachment of PEG to DNA/PEI complexes improves DNA delivery in vivo. See abstract and first paragraph on page 595, column 1. It would have been similarly obvious to optimize the N/P ratio of a nucleic acid complex comprising the lipopolymer, as well as the amount of targeting ligand incorporated into the complex, as each of these will clearly affect the performance of the complex.

Claims 12-15, 17-21, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Epand et al (US Patent 5,283,185, issued 2/1/94) in view of Godbey et al (J. Contr. Rel. (1999) 60: 149-160).

Epand taught methods and lipopolymeric compositions for transferring nucleic acids into cells. See abstract, claims 1 and 10, and compound XV, described at column 9, lines 45-58. Lipopolymeric compound XV is formed by mixing cholesteryl chloroformate with PEI 600. The resulting reaction chemistry is identical to that taught in the instant application, and results in the formation of a lipopolymer with cholesterol covalently bound to PEI via an ester linkage. Compare Fig. 1 of the instant application with Fig. 3 of Epand. The composition may comprise a DOPE helper lipid in a 1:1 ratio with the cationic lipopolymer. See Table I at column 12, and column 12, lines 58-61. Epand teaches that the charge ratio of lipopolymer to nucleic acid is a result effective variable. See column 13, lines 6-11, and Fig. 5.

Epand did not teach PEI covalently modified with a biocompatible hydrophilic polymer or a targeting ligand.

Godbey taught that PEI may be covalently modified with PEG for the purpose of extending its half life in vivo. See paragraph bridging columns 1 and 2 on page 153. Additionally, Godbey teaches that PEI has been coupled to a variety of ligands for the purpose of cell targeting, including galactose and transferrin, and notes that ligands which have been successfully used in poly(L-lysine)/DNA complexes should be useful in PEI/DNA complexes as well. Such ligands include low density lipoprotein. See paragraph bridging pages 154 and 155. Godbey reviewed the use of PEI in gene delivery methods, and noted that PEIs ranging in molecular weight from about 8000 to about 1,000,000 are useful for gene delivery. See page 121, paragraph bridging columns 1 and 2; and Fig. 2 on page 151. Godbey also taught that the molecular weight of PEI in such complexes is a result-effective variable, and that the ratio of PEI amine to DNA phosphate is also a result-effective variable. See page 153, column 1, second and third full paragraphs; and lines 1-6 of the paragraph bridging pages 153 and 154.

It would have been obvious to one of ordinary skill in the art the time of the invention to covalently modify the PEI of Epand with PEG in order to increase its half life in vivo, and to attach targeting ligands to PEI in order to improve the specificity of nucleic acid delivery. It would have been similarly obvious to optimize the N/P ratio of a nucleic acid complex comprising the lipopolymer, as well as the amount of targeting

ligand incorporated into the complex, as each of these will clearly affect the performance of the complex.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,696,038. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

With regard to instant claims 1-11, note that claim 2 of '038 is drawn to a biodegradable cationic lipopolymer comprising a branched polyethylenimine (PEI) a $C_{12}$ to $C_{18}$ fatty acid, and a biodegradable linker, wherein the biodegradable linker covalently

links the branched PEI and the $C_{12}$ to $C_{18}$ fatty acid and wherein the cationic lipopolymer further comprises a targeting moiety. The specification of '038 indicated that the term "linker" included PEG (see column 8, lines 5-8). As such it would have been obvious to use PEG to link PEI and $C_{12}$ to $C_{18}$ fatty acid to make a cationic lipopolymer. The '038 specification discloses esters as suitable covalent linkages. See column 3, lines 17-21. PEG may be in the range of 0.5-20 kDa, see column 8, lines 13-15. The ratio of PEG to PEI is considered to be routinely optimized by those of ordinary skill in the art. The targeting moieties recited in instant claim 9 are set forth in '038 claim 2, and the ratio of targeting ligand to lipopolymer is considered to be obvious to optimize.

With regard to claims 12-21, Claim 1 of '038 is drawn to the cationic lipopolymer poly{(ethylene imine)-co-[N-2-aminoethyl ethylene imine]-co-[N-(N-cholesteryloxy-carbonyl-(2-aminoethyl))ethylene imine]}("PEACE"), and so discloses a species of the genuses claimed in instant claims 12, 14, 15, and 17.

Pertinent to instant claim 13, the portion of the specification supporting the claims indicates that the PEI may be within the weight range of 600 Da to 25 kDa. See column 7, lines 33-35.

Claim 5 of '038 is drawn to PEACE grafted with PEG of between 500 and 20,000 Da and so discloses a species of the genuses claimed in instant claim 16.

Claim 12 of '038 is drawn to PEACE in which PEI is covalently modified with both PEG and a targeting moiety, as in instant claims 18-21. The targeting moieties of instant claim 19 are set forth in '038 claim 7.

Although '038 does not claim any particular ratio of targeting ligand to PEI, it would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the amount of targeting ligand incorporated into the complex, as this would clearly affect the performance of the lipopolymer.

Claims 22-27 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,696,038, as applied to claims 1-21 above, and further in view of Epand (US Patent 5,283,185, issued 2/1/94). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

The claims of '038 are discussed above. '038 does not claim complexes of cationic lipopolymers with nucleic acids, or helper lipids.

Epand taught methods and lipopolymeric compositions for transferring nucleic acids into cells. See abstract, claims 1 and 10, and compound XV, described at column 9, lines 45-58. Lipopolymeric compound XV is formed by mixing cholesteryl chloroformate with PEI 600. The resulting reaction chemistry is identical to that taught in the instant application, and results in the formation of a lipopolymer with cholesterol covalently bound to PEI via an ester linkage. Compare Fig. 1 of the instant application with Fig. 3 of Epand. The composition may comprise a DOPE helper lipid in a 1:1 ratio with the cationic lipopolymer. See Table I at column 12, and column 12, lines 58-61. Epand taught that the charge ratio of lipopolymer to nucleic acid is a result effective variable. See column 13, lines 6-11, and Fig. 5.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the cationic lipopolymers of '038 to form complexes with nucleic acids to transfect cells. One would have been motivated to do so because Godbey taught that structurally similar compounds were used for that exact purpose. It would have been obvious to optimize the N/P ratios of the complexes because Epand taught that this ratio was a result-effective variable.

## *Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635